The Importance of Prognostic Factors in Premenopausal Women with Breast Cancer

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Abstract. *Background: Basic conventional prognostic factors for breast cancer include the age of the patient, tumor grade, regional lymph nodes status, and estrogen (ER) and progesterone (PR) receptor status. Positivity of the HER2 receptor (c-erbB-2) seems to be a new prognostic and predictive factor. Prognostic factors seem to be more important in the high-risk group of the premenopausal females. We evaluated individual prognostic factors (age, histology, TNM classification, ER, PR, CA 15-3, CEA, HER2) and their impact on disease-free survival (DFS) and overall survival (OS) during the 5-year follow-up period. Patients and Methods: Forty-two patients were monitored after standard oncology treatment for a period of at least 5 years. The statistical significance of the individual prognostic parameters was evaluated in relationship to the time to progression (DFS and OS). Results: The following were evaluated as statistically significant prognostic parameters for DFS: PR positivity (p=0.0036), proliferative marker MIB1 (p=0.0108), pre-operative level of CA 15-3 (p=0.0425), ER negativity (p=0.0507). The following were evaluated as statistically significant prognostic parameters for OS: PR positivity (p=0.0003), MIB1 (p=0.0005), ER (p=0.0440), pre-operative level of CEA (p=0.0495). Positivity of immunohistochemically performed test of c-erbB-2 was not statistically significant for DFS os OS (p=0.6361 and 0.9323, respectively). Conclusion: The statistically significant prognostic importance of the levels of tumor markers CA 15-3 and CEA for prognosis in breast cancer of premenopausal females was proven. So far, these factors have been underestimated. The prognostic parameters of ER, PR and MIB1 were statistically significant. While no prognostic importance was confirmed for c-erbB-2 positivity; this factor cannot be evaluated in premenopausal females separately from the other prognostic factors due to the predictive value in relation to the adjuvant therapy (patients with HER+, ER+, PR–).*

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Breast carcinoma is the most common malignancy in women in industrially developed countries. According to statistical estimates, 211,240 cases of detected breast carcinomas and 40,410 deaths associated with this diagnosis were expected for 2005. The latest available data for the Czech Republic are from 2002 when 5,378 cases of this disease were diagnosed and 1,965 patients died (1, 2, 6, 7).

The main risk factors for the origin of breast carcinoma are female gender, advanced age, early menarche, late menopause, nulliparity, older age at first birth, family history of breast cancer, personal history of proliferative benign breast disease, history of radiation exposure. Risk factors also include *BRCA-1*, *BRCA-2*, *p53* or *PTEN* mutations and current or prior oestrogen or progesterone hormone replacement therapy (1, 3, 4, 14, 15, 18).

Approximately one third of breast carcinoma patients are affected in the premenopausal period. Breast carcinoma represents a much higher risk to premenopausal women, particularly to those who became ill before their 35th year of age. The disease takes a much more aggressive course and the prognosis is worse (5, 6).

Prognostic factors are given for women with breast carcinoma irrespective of their relation to menopause. Any measurable data about patients which were acquired during surgical performance (determination of diagnosis) and which are connected with the results of the treatment (overall survival, disease-free survival or local control) are considered to be prognostic factors (1, 7). The study of prognostic factors faces two basic problems. The first consists of differences in the assessment and interpretation of the laboratory results and often even in the definitions of basic terms, such as progression (13). The second problem is the lack of large multicentre studies for the investigation of

prognostic factors. Looking for predictive factors (connected with certain therapies) is much more interesting, and it is often believed naively that we will gain information about the optimal therapeutic procedure through the assessment of a single parameter in such an undoubtedly complicated entity as a heterogenous tumor. There is another considerable problem, namely downplaying negative results in the search for prognostic factors and the excessive overrating of positive results (11).

premenopausal patients are a high-risk group. Although they represent only 30% of all patients with breast carcinoma, these young patients make a substantial contribution to the statistics of therapeutic failure (1, 2, 4, 5). Prevention of the disease progression is the principal aim of adjuvant therapy. Breast carcinoma relapse (except for local relapses) can often be treated through long-term therapy, but basically it is incurable and leads to the patient's ultimate death. Table I shows the historical prognostic factors. New data on the essential prognostic role of HER2/neu positivity, MIB1 tumor proliferation activity (which measures the percentage of cells in the G1-phase of the cellular cycle), the role of the plasminogen activator system and other molecular and genomic factors have recently been published (12, 13, 19, 20).

In 2005, Professor Goldhirsch presented the conclusions of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. He designated risk categories of patients for disease relapse, where HER2/neu positivity, together with negative post-operative lymph nodes, constituted a medium risk, and HER2/neu positivity together with positive lymph nodes counted as a high risk of disease recurrence and was therefore suggested as one of the main prognostic factors (1, 2, 11, 19).

The aim of our study was to determine the significance of prognostic signs for overall survival and disease-free survival of premenopausal patients treated in our centre with similar therapeutic methods.

Patients and Methods

Forty-two premenopausal patients who had undergone standard oncological treatment were monitored for a period of at least 5 years (minimum follow up 5 years). We monitored the statistical significance of levels of individual prognostic signs (age, histology, TNM classification, MIB1 proliferation index, positivity of ER and PR steroid receptors, CA 15-3, CEA, HER-2) in relation to disease-free (DFS) and overall survival (OS). The average age of the patients was 43.8 years, ranging from 31 to 50 years. Thirty-four patients had positive ER or PR (ER and/PR >10%), 19 patients were c-erbB-2 positive (immunohistochemistry 3+), MIB1 ranges were between 5% and 55%. Histological tumor types were as follows: 32 ductal invasive carcinomas, 8 lobular carcinomas, and 2 other types of cancer (angiosarcoma, cystosarcoma phyloides).

Fifteen patients had T1 tumors (35.71%), 20 had T2 tumors (47.62%), 2 T3 tumors (4.76%) and 5 had T4 tumors (11.9%).

Table I. *Historical prognostic factors.*

Host	Tumor
Age	Size
Menstruation cycle	Grade
Inflammatory response	Vascular invasion
Associated disease *in situ*	Involvement of lymph nodes
	DNA content
	(ploidity, S-phase)

Fourteen patients had negative axillary glands N0 (30.95%), 24 N1 (57.14%) and 5 N2 (11.9%). Twenty-nine (69%) patients had I and II stage of disease. No patient had distant metastases at the time of diagnosis. The treatment corresponded with the stage of the disease. Patients with T1 and T2b tumors were operated on, and the surgery was followed by 6 cycles of FAC (fluorouracil, doxorubicin, cyclophosphamide) adjuvant chemotherapy. Patients with breast-conserving surgery or with more than 3 positive axillary glands were subsequently treated with radiotherapy (chest wall and lymphatics). Patients with positive ER or PR (more than 10% positive cells) started ablative hormonal treatment after chemotherapy (ovariectomy, LH-RH analogues + tamoxifen). Patients with tumors larger than T2 were treated with 3 cycles of neoadjuvant FAC chemotherapy, followed by surgery, radiotherapy (chest wall and lymphatics), and then continued with adjuvant chemotherapy of an identical FAC cycle (6 cycles). Patients with positive ER or PR (more than 10% cells) started hormonal treatment after finishing chemotherapy. Formalin-fixed, parafin-embedded sections were examined, using the following commercial kits: c-erbB-2/HER-2 oncoprotein (recombinant protein directed against the external domain of c-erbB-2 oncoprotein molecule, Novocastra Ltd, UK), ER, PR (monoclonal antibodies, Immunotech), and MIB1 antibody (Anti-human Ki-67 antigen, DAKO).

Results

The prognostic influence of individual factors on DFS is shown in Table II. Factors statistically leading to a shorter DFS are low PR positivity, high MIB1, high post-operative CA 15-3, low ER values, N2 (N0 and N1 behave identically from a DFS point of view), high post-operative CEA, old age, HER2 (behaving similarly from the DFI point of view). T4 is the worst for DFS, T3 is the best, T2 and T3 do not differ (but there are not sufficient data for T3 and T4).

In multivariate analysis, PR and MIB1 have an influence on DFI as independent prognostic factors (according to decreasing Chi-square scores), and the PHREG procedure (in S.A.S. program, version 8.22). The reason why multivariate analysis does not yield significant ER values and post-operative CA 15-3 concentrations is that there is a strong correlation between ER and PR, and post-operative CA 15-3 correlation with the N status.

The influence of individual prognostic factors on the OS of patients is described in Table III.

Table II. *Prognostic influence of individual factors on disease-free interval (DFI).*

Variable	test	Standard statistic	Chi-square deviation	*P*> Chi-square	
1	PR	348.4	119.8	8.4662	0.0036
2	MIB1	–138.6	54.3594	6.5023	0.0108
3	CA 15-3 post op.	–23.1733	11.4143	3.8009	0.0425
4	ER	218.5	114.8	3.6218	0.0507
5	N status	–1.3825	0.9022	2.4767	0.8783 NS
6	CEA post op.	–0.8463	0.7617	1.1011	0.1505 NS
7	Age	–13.4018	14.3225	0.8756	0.3494 NS
8	Histology	–2.5947	3.3729	0.5918	0.4417 NS
9	Her 2 *neu*	2.2070	4.4433	0.2467	0.6194 NS
10	T status	–0.3982	2.6014	0.0234	0.8783 NS

Rank tests for the association of DFI with covariates. Univariate Chi-squares for the Wilcoxon Test.

Table III. *The influence of individual prognostic factors on the overall survival (OS) of patients.*

Variable	test	Standard statistic	Chi-square deviation	*P*> Chi-square	
1	PR	367.3	102.6	12.8068	0.0003
2	MIB1	–153.3	43.7954	12.2524	0.0005
3	ER	196.5	97.5607	4.0560	0.0440
4	CEA post op.	–1.4510	0.7528	3.9148	0.0495
5	Histology	–5.9050	3.8498	3.2936	0.0583
6	CA 15-3 post op.	–31.2025	20.2158	2.3823	0.1227 NS
7	N status	–2.5742	1.7373	2.1955	0.4129 NS
8	Age	17.5376	13.3315	1.7306	0.1883 NS
9	T status	–1.8949	2.3141	0.6705	0.4129 NS
10	Her 2 *neu*	0.9048	3.5820	0.0590	0.8081 NS

Rank tests for the association of OS with covariates. Univariate Chi-squares for the Wilcoxon test.

The factors that lead to a statistically shorter OS are: low PR values, high MIB1, low ER, high post-operative CEA.

In multivariate analysis, the values of PR, MIB1 and ER have an influence on OS as independent prognostic factors (according to decreasing Chi-square score), and the PHREG procedure (in S.A.S. program, version 8.22) attempted to add age – but this was already an insignificant contribution. The reason for an absence of a post-operative significance of CEA in the multivariate analysis is that there is an insignificant correlation of post-operative CEA with PR, ER and MIB1.

Discussion

We demonstrated a statistically significant prognostic contribution of CA 15-3 and CEA for the determination of breast cancer prognosis in premenopausal patients. These factors have been unjustifiably undervalued. PR negativity, a high proliferation index of MIB1, high post-operative CA 15-3 values and ER negativity have a negative prognostic influence on time to progression. High levels of post-operative CEA values have a negative prognostic influence on OS. They suggest either a non-radically performed surgery or a hidden generalization of the disease at the time when the diagnosis was first determined. The most important positive prognostic factors seem to be PR positivity and a low level of MIB1. These demonstrate the importance of ablative therapy in premenopausal patients, and the question is only when this therapy will replace the present application of chemotherapy. The prognostic factors we determined differ from those commonly published (16, 21, 22). There is an interesting absence of any influence of c-erbB-2 positivity. The prognostic influence of c-erbB-2 positivity would probably have to be demonstrated on a larger group of patients. In premenopausal patients, it is impossible to assess c-erbB-2 positivity separately from other prognostic factors because of its predictive response in relation to adjuvant therapy (HER-2 +, ER+, PR– patients) (17). The question remains whether the historical prognostic factors are equally applicable to both premenopausal and post-menopausal patients with breast carcinoma and whether these factors should be monitored separately, in accordance with patients' relation to menopause. However, in order to acquire valid data, a large multicentre study and a complete genetic assessment of all samples would be necessary (8, 9).

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